

111-1090²⁰
DA/C Forbts

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,757,057

#24

Patentees: Fernando Fussi
Gianfranco Fedeli

Assignee: Pharmacia & Upjohn Aktiebolag

Issue Date: July 12, 1988

Filing Date: January 7, 1986

RECEIVED
JUL 21 1997
OFFICE OF PETITIONS
A/C PATENTS

REQUEST AND APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. 156 FOR U.S. PATENT NO. 4,757,057

Assistant Commissioner for Patents
ATTENTION: BOX PATENT EXTENSION
Washington, DC 20231

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PATENT EXTENSION
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Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984 and, as amended, 35 U.S.C. § 156, Pharmacia & Upjohn Aktiebolag, owner of the above-identified patent by an assignment recorded on August 4, 1978 at Reel 3571, Frame 836, to Hepar Chimie S.A. (Exhibit 1); subsequent change of corporate name recorded on March 13, 1997, at Reel 8382, Frame 0242 to Kabi Pharmacia AB (Exhibit 2); subsequent change of corporate name filed with the U.S. Patent and Trademark Office on June 25, 1997, to Pharmacia Aktiebolag (Exhibit 3); and subsequent merger filed with the U.S. Patent and Trademark Office on June 26, 1997, to Pharmacia & Upjohn Aktiebolag (Exhibit 4); hereby requests an extension of the patent term of U.S. Patent No. 4,757,057. The following information is submitted in

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accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*, and follows the numerical format set forth in 37 C.F.R. § 1.740(a).

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is ardeparin sodium injection and will be sold under the trademark Normiflo in the United States.

The approved product has the following physical structure and characterization:

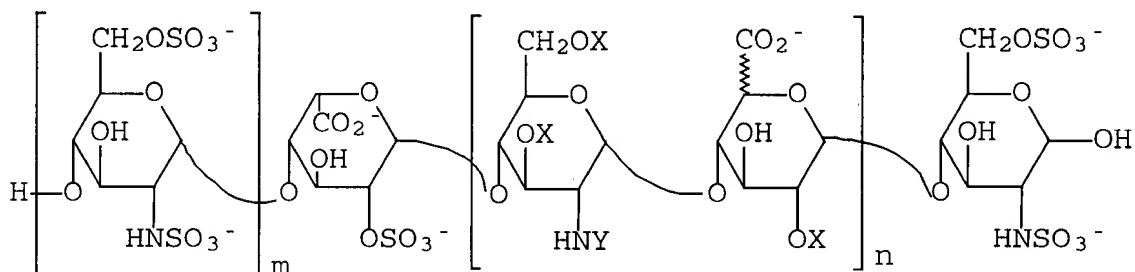
The established generic names of the subject material are RD Heparin Sodium; low molecular weight heparin sodium; and ardeparin sodium.

The descriptive chemical name of the subject material is polymers of derivatives of D-glucosamine (N-sulfated, N-acetylated, and/or O-sulfated) and hexuronic acid (L-iduronic acid or D-gluconuronic acid; including O-sulfated derivatives).

The low molecular weight heparin code numbers are WY-90,493 and WY-90,505.

Relative molecular mass: The average relative molecular weight is from 5,500 to 6,500 Daltons, not less than 98% percent of which falls within 2,000-15,000 Daltons.

Structural formula: The structural formula is as follows:



$m=0$ or 1 ,
 $n=7-9$,
 $X=H, SO_3^-$,
 $Y=SO_3^-, COCH_3$.

The above information is confirmed by Exhibit 12, a portion of the NDA as submitted.

(2) A complete identification of the Federal statute, including the applicable provision of law under which regulatory review occurred:

The regulatory review occurred under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FFDCA) and Title 21 of the Code of Federal Regulations (C.F.R.), Part 314.50. Section 505 of FFDCA provides for the submission and approval of new drug applications (NDA's) for human drug products meeting the

definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing, or use under the provision of law under which the applicable regulatory review period occurred:

Normiflo (ardeparin sodium) injection was approved by the Food and Drug Administration (FDA) for manufacture and import into the United States for commercial marketing (sale, barter, or exchange) pursuant to Section 505 of the FFDCA on May 23, 1997 (see letter from FDA, Exhibit 5, and chronology, Exhibit 7).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved:

As stated in Sections 1, 2, and 3 above, the active ingredient in the product is Normiflo (ardeparin sodium) injection. Normiflo (ardeparin sodium) injection had not previously been approved for commercial marketing or use under

the Federal Food, Drug and Cosmetic Act until May 23, 1997.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to Section 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on May 23, 1997 (Exhibit 5 and Exhibit 7), and the last day within the sixty-day period for submission of an application for extension of patent is July 22, 1997. This application is timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue and the date of expiration:

U.S. Patent No.:	4,757,0557
Inventors:	Fernando Fussi Gianfranco Fedeli
Issued:	July 12, 1988
Expires:	July 12, 2005 (17 years from the grant)

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent is attached as Exhibit 6.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment or reexamination certificate issued in the patent:

a copy of the receipt issued by the U.S. Patent and Trademark Office of the first maintenance fee payment is attached hereto as Exhibit 8; a copy of a statement issued by computer Patent Annuities confirming payment of the second maintenance fee is attached hereto as Exhibit 9; and no disclaimer, certificate of correction, or reexamination certificate has issued.

(9) A statement that the patent claims the approved product or method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent No. 4,757,057 claims a method of increasing the antithrombotic activity of mammalian blood by administering the approved product to a mammal in need of treatment for thrombosis.

Normiflo (ardeparin sodium) injection is described above in section (1).

Claim 1 of U.S. Patent No. 4,757,057 is directed to a method

of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity. According to the method, an oligoheteropolysaccharide is administered to a mammal in need of treatment for thrombosis. The oligoheteropolysaccharide includes depolymerized heparin containing sulfate groups in the quantity and in the positions characteristic of heparin. The oligoheteropolysaccharide has the following physico chemical properties: an average molecular weight (determined with the Somogy method in comparison with commercial heparin) of from 2600 to 5500 daltons; hexosamines after hydrolysis (reaction with p-dimethyl-amino benzaldehyde) of $28\% \pm 2\%$; uronic acids after hydrolysis (reaction with carbazol) of $31\% \pm 4\%$; organic SO_4^- after hydrolysis (titration with naphtharsone) of $30\% \pm 4\%$; molar ratios of uronic acids/hexosamines/ $\text{SO}_4^- = 1/1/2$; specific rotatory power of the aqueous solution $[\alpha]_D^{20} = +40^\circ - +50^\circ$; electrophoresis on cellulose acetate (pyridine/acetic acid/water (1:10:299)) pH 4.5 and development with toluidine blue resulted in a single band with anodic mobility $U = 2.1 \times 10^{-4} \text{ cm}^2 \text{ v}^{-1} \text{ sec}^{-1}$; powder of ivory color, amorphous and slightly hygroscopic; aqueous solution clear or slightly opalescent; and pH of 5% aqueous solution of 7-8.

Claim 2 is directed to a method of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity. According to the method, an oligoheteropolysaccharide is administered to a mammal in need of treatment for thrombosis. The oligoheteropolysaccharide includes

depolymerized heparin having an average molecular weight of about 2600 to about 5500 daltons determined by the Somogy method in comparison with commercial heparin and having sulfate groups in the quantity and in the positions characteristic of heparin. The oligoheteropolysaccharide displays greater antithrombotic activity than anticoagulant activity.

Claim 3 is directed to a method of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity. The method includes administering to a mammal an effective amount of a therapeutical composition for the prevention of thrombosis. The composition contains as the active ingredient the oligoheteropolysaccharide described in claims 1 or 2.

The marketing authorization covers a product, Normiflo (ardeparin sodium) injection, for use in prophylaxis of thrombosis. This is covered by claims 1-3.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug product, antibiotic, or human biological, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug, the date a major health or environmental effects test on the drug was initiated and any available substantiation of the date of the date of an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; the date on which a new animal drug application (NADA) was initially submitted and the NADA number; and the date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product, the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; the date an application for a license was submitted under the Virus-Serum-Toxin Act; and the date the license issued;

(iv) For a patent claiming a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug and Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published a FEDERAL REGISTER notice listing the additive for use;

(v) For a patent that claims a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available substantiation of that date; the date on which an application for product approval of notice of completion of a product development protocol under Section 515 of the Federal Food, Drug and Cosmetic Act was initially submitted and the number of the application or protocol; and the date on which the application was approved or the protocol declared to be completed.

On September 21, 1987, Wyeth-Ayerst Laboratories, licensee of patent 4,757,057, submitted a investigational new drug (IND) application. The IND became effective on September 21, 1987. On September 28, 1987, FDA assigned the IND No. 30,639. Wyeth-Ayerst Laboratories initially submitted a new drug application (NDA) to FDA on February 28, 1992. FDA subsequently assigned the

NDA No. 20-227. FDA approved the NDA in a letter dated May 23, 1997. This chronology is set forth in Exhibit 7 attached hereto.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Wyeth-Ayerst Laboratories, in its role as licensee, was actively involved in obtaining FDA approval for Normiflo (ardeparin sodium) injection. As discussed in Section 10 above, on September 21, 1987, Wyeth-Ayerst Laboratories, licensee of patent 4,757,057, submitted an investigational new drug (IND) application. The IND became effective on September 21, 1987. On September 28, 1987, FDA assigned the IND No. 30,639. The initial submission date of the NDA was February 28, 1992. The NDA was approved on May 23, 1997.

Numerous contacts and meetings occurred between Wyeth-Ayerst Laboratories and FDA with respect to approval. Exhibit 7 illustrates significant activities undertaken with respect to Normiflo (ardeparin sodium) injection during the regulatory review period.

(12) A statement beginning on a new page that, in the opinion of the applicant, the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.

(a) Statement of eligibility of the patent for extension under 35 U.S.C. § 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) except for certain products, the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 4,757,057 expires on July 12, 2005, in view of 35 U.S.C. § 154, as amended (i.e., 17 years from the patent grant dated July 12, 1988). This application has therefore been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, Pharmacia & Upjohn Aktiebolag, owner of the above-identified patent by an assignment recorded on August 4, 1978 at Reel 3571, Frame 836, to Hepar Chimie S.A. (Exhibit 1); subsequent change of corporate name recorded on March 13, 1997, at Reel 8382, Frame 242 to Kabi Pharmacia AB (Exhibit 2); subsequent change of corporate name filed with the U.S. Patent and Trademark Office June 25, 1997, to Pharmacia Aktiebolag (Exhibit 3); and subsequent merger filed with the U.S. Patent and Trademark Office June 26, 1997, to Pharmacia & Upjohn Aktiebolag (Exhibit 4).

This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date, May 23, 1997, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. § 156(d).

(4) As evidenced by the attached chronology (Exhibit 7),

the product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of Normiflo (ardeparin sodium) injection after regulatory review under Section 505(b)(1) of the FFDCA is the first permitted commercial marketing of Normiflo (ardeparin sodium) injection. This is confirmed by the absence of any approved new drug application or license product application for Normiflo (ardeparin sodium) injection prior to May 23, 1997.

(b) Statement as to length of extension claimed:

The term of patent number 4,757,057 should be extended by 1820 days to expire on July 12, 2010. This extension was determined on the following basis, as documented on the attached Calculation Of Length Of Patent Term Extension For A Human Drug Product (Exhibit 10): as set forth in 35 U.S.C. § 156(g)(1) and 37 C.F.R. § 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND (September 21, 1987) and the initial submission of the NDA (February 28, 1992), a period of 1621 days, plus the length of time between the initial date of the submission of the NDA (February 28, 1992) to NDA approval (May 23, 1997), a period of 1620. These two periods added together equal a period of 3241 days.

Pursuant to 35 U.S.C. § 156(c) and 37 C.F.R. § 1.775(d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs on and after the date the patent was issued. In this case, this is a period running from the date of the effective date of the initial IDA, September 21, 1987, to the date of the NDA approval, May 23, 1997, a period of 3241 days. The patent issued July 12, 1988. Therefore, the regulatory review process of 3241 days should be shortened by a period of 294 days to a period of 2947 days.

The revised regulatory review process of 2947 days should also be reduced by a number of days equal to one-half of the length of time between the effective date of the initial IND (September 21, 1987) and the initial submission of the NDA (February 28, 1992), a period of 1621 days, minus the number days of this 1621 day period that occurred prior to the issuance of the patent, a period of 294 days. The revised regulatory review period so calculated is 2283 days.

As discussed in paragraph (11) above, and as illustrated in Exhibit 7, Pharmacia & Upjohn Aktiebolag, through its licensee, Wyeth-Ayerst Laboratories, was continuously and diligently working toward securing FDA approval for Normiflo (ardeparin sodium) injection. As Pharmacia & Upjohn Aktiebolag through its licensee, Wyeth-Ayerst Laboratories, acted with due diligence

during the entire period of regulatory review, the 3241 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. § 156(c)(1) or 37 C.F.R. § 1.775(d)(1)(ii).

Pursuant to 35 U.S.C. § 156(c)(3) and 37 C.F.R. § 1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval (May 23, 1997 to July 12, 2005, a period of 2972 days), when added to the revised regulatory review period of 2283 days exceeds 14 years, a period of 5110 days, the period of extension must be reduced, so that the total of both such periods does not exceed 14 years. In this case, the total of the period remaining in the term of the patent after the date of approval plus the revised regulatory review period, a total period of 5255 days, exceeds 14 years and, therefore, the 2283 days of the revised regulatory period should be reduced.

The period of the extension also cannot exceed a number of days equal to five years beyond the original expiration date of the patent, in this case to a date of July 12, 2010. In this case, the 2283 day revised regulatory review process exceeds the five year limit. Therefore, the patent term should be extended for a period of 1820 days, the number of days equal to five years.

(13) The statement that applicant acknowledges a duty to

disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought (see Section 1.765):

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services and the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension of the term of U.S. Patent 4,757,057 (see Section 1.20(n)):

As indicated by the letter of transmittal submitted with this application, a check for the filing fee is attached. In addition, the Commissioner of Patents and Trademarks is hereby authorized to charge any fees connected with this communication to Deposit Account No. 22-0185 in the name of Pollock, Vande Sande & Priddy.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Address all correspondence to:

Burton A. Amernick
Pollock, Vande Sande & Priddy
1990 M Street, N.W., Suite 800
P.O. Box 19088
Washington, DC 20036

(202) 331-7111.

(16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. § 156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

(17) An oath or declaration as set forth in 37 C.F.R. § 1.740(b) :

As the undersigned attorney (by authority of the attached general power of attorney (Exhibit 11) signed by Mr. Fredrik Berg, Company Secretary of Pharmacia & Upjohn Aktiebolag) for Pharmacia & Upjohn Aktiebolag, the owner of U.S. Patent No. 4,757,057, which, by submission of this paper and attached exhibits, now applies for an extension of term of this patent, I, Mr. Burton A. Amernick, attorney for Pharmacia & Upjohn Aktiebolag, declare that:

(1) I am Burton A. Amernick, attorney for Pharmacia & Upjohn Aktiebolag and have general authority from Pharmacia & Upjohn Aktiebolag to act on its behalf in patent matters as evidenced by the attached power of attorney signed by Mr. Fredrik Berg, Company Secretary of Pharmacia & Upjohn Aktiebolag;

(2) I have reviewed and understand the contents of the attached application for extension of the term of U.S. Patent No. 4,757,057;

(3) I believe the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(4) I believe the length of extension of the term of U.S. Patent No. 4,757,057 claimed is fully justified under 35 U.S.C. § 156 and applicable regulations; and

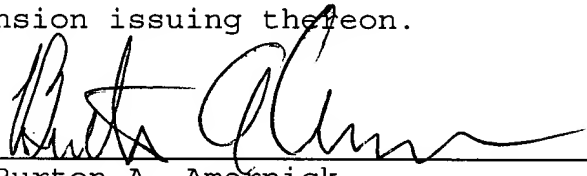
(5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

Date:

July 21, 1997



Burton A. Amernick
Registration Number 25,842
Attorney for Pharmacia & Upjohn AB
Pollock, Vande Sande & Priddy
1990 M Street, NW, Suite 800
Washington, DC 20036

(202) 331-7111

Best Available Copy

Assignment

EXHIBIT

ALL-STATE® INTERNATIONAL

Ubertas, we, Fernando FUSSI and Gianfranco FEDELI

of LESMO and MILAN

State of Italy

we VS

invented new and useful improvements

in "Oligo-heteropolysaccharides having a heparin-like activity method for their preparation and pharmaceutical compositions based thereon"

for which we are about to make an

application for

Letters Patent of the United States:

And Ubertas, HEPAR CHIMIE S.A.

of FRIBOURG

State of Switzerland

is desirous of acquiring an interest therein and in the

Letters Patent to be obtained thereof:

Now Therefore, be it known by all whom it may concern, that for and in consideration of one Dollar (\$ 1.00) and other good and valuable consideration to US in hand paid, the receipt of which is hereby acknowledged, we have assigned, sold and set over, and by these presents do assign, sell, and set over unto the said HEPAR CHIMIE S.A.

for the territory of the United States of America and not elsewhere, the entire

title and interest in and to the said invention, and said application, prepared and executed by us

on July 25

1978, filed

Serial No.

preparatory to obtaining Letters Patent therefor; said invention, application and Letters Patent to be held and enjoyed by the said HEPAR CHIMIE S.A.

as fully and entirely as the same would have been held by us had this assignment and sale not been made.

AND we hereby covenant and agree that we will at any time upon the request and at the expense of said assignee execute and deliver any and all papers and do all lawful acts that may be necessary or desirable to perfect the title to said invention and to obtain Letters Patent therefor, and we hereby authorize and request the Commissioner of Patents to issue the said Letters Patent to the said HEPAR CHIMIE S.A.

In accordance with this assignment.

In Testimony Whereof, we hereunto set our hand at MILAN

State of Italy this 25th day of July

1978

Fernando Fussi
Gianfranco Fedeli

Serial No.

931,215

RECEIVED
3571
836

RECORDED
JAN 11 1979
FBI - NEW YORK
FBI - NEW YORK
FBI - NEW YORK


PATENT
REEL: 8382 FRAME: 0242

ASSIGNMENT

We, Hepar Chimie S.A., a company incorporated under the laws of Switzerland, do hereby declare that we are the owner of the US Patent No 4757057 and that we have assigned the rights and interests in said patent to Kabi Pharmacia AB, a company incorporated under the laws of Sweden, of S-751 82 Uppsala, Sweden.

Dated this 29 day of November, 1991

HEPAR CHIMIE S.A.



Martin Zinnenlauf

Serial No. 4,757,057

Docket No. 0151/00184

Applicant:

Resp./Bill Atty: BAA

Due Date: ---

The following was/were received in the U.S. Patent and Trademark Office on the date stamped hereon.

<input type="checkbox"/>	Amendment (or Response)	<input type="checkbox"/>	IDS with 1449, refs
<input type="checkbox"/>	Petition for -Mo. Ext. of Time	<input type="checkbox"/>	Issue Fee Transmittal
<input type="checkbox"/>	Response to Restriction Req.	<input type="checkbox"/>	Notice of Appeal
<input type="checkbox"/>	Response to Missings Parts	<input type="checkbox"/>	Appeal Brief
<input type="checkbox"/>	Executed Declaration or POA	<input type="checkbox"/>	Maintenance fee transmittal
<input type="checkbox"/>	Priority Document(s)	<input type="checkbox"/>	Request for Refund
<input checked="" type="checkbox"/>	Assignment(s) & cover sheet	<input type="checkbox"/>	Request for corrected Filing Receipt
<input type="checkbox"/>	Req. to Approve Drawing Changes	<input checked="" type="checkbox"/>	Other: Request for expedited recordal
<input type="checkbox"/>	Sheets formal drawings	<input checked="" type="checkbox"/>	Check No. <u>20616</u> for \$70



ALL-STATE INTERNATIONAL

EXHIBIT

LAW OFFICES

POLLOCK, VANDE SANDE & PRIDDY, R.L.L.P.

INTELLECTUAL PROPERTY CAUSES

SUITE 800, 1990 M STREET, N.W.

WASHINGTON, D.C. 20036-3425

TELEPHONE (202) 331-7111

FAX (202) 293-6229

FAX (202) 223-2596

MAIL ADDRESS:

P.O. BOX 19088

WASHINGTON, D.C. 20036-0088

E-MAIL: pvsp@pvsp.com

ELLIOTT I. POLLOCK
GEORGE VANDE SANDE
ROBERT R. PRIDDY
RICHARD WIENER
BURTON A. AMERNICK
STANLEY B. GREEN
MORRIS LISS
TOWNSEND M. BELSER, JR.
MARTIN ABRAMSON

GEORGE R. PETTIT
THOMAS J. VANDE SANDE
LOUIS WOO
ELZBIETA CHLOPECKA
ERIC J. FRANKLIN
ROBERT SCOTT WALES*
JEFFRI A. KAMINSKI*

*Not admitted in the District of Columbia

June 26, 1997

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

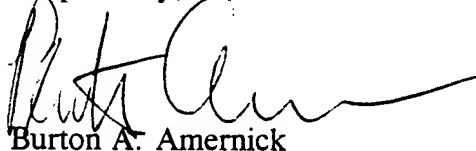
Re: Request for Expedited Recordal Service

Dear Sir:

It is hereby requested that the attached document be recorded on an expedited basis.
A check covering the recordal fee plus the fee for expedited service is attached.

The Commissioner is authorized to charge any deficiency or credit any overpayment
to Deposit Account No. 22-0185. A duplicate authorization is attached.

Respectfully,


Burton A. Amernick

BAA/dlb

Encls.

LAW OFFICES

POLLOCK, VANDE SANDE & PRIDDY, R.L.L.P.

INTELLECTUAL PROPERTY CAUSES

SUITE 800, 1990 M STREET, N.W.
WASHINGTON, D.C. 20036-3425
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MORRIS LISS
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*Not admitted in the District of Columbia

June 25, 1997

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Respectfully,



Burton A. Amernick

BAA/dlb
Encls.

Form PTO-1595

Recordation Form Cover Sheet

U.S. Department of Commerce

1-31-92

PATENTS ONLY

Patent and Trademark Office

To the Honorable Commissioner of Patents and Trademarks:

Please record the attached original documents or copy thereof.

1. Name of conveying party(ies)
Kabi Pharmacia AktiebolagAdditional name(s) of conveying party(ies)
attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger
☐ Security Agreement ☒ Change of
name
☐ Other

Execution Date: December 2, 1993

2. Name and address of receiving party(ies):

Name: Pharmacia Aktiebolag
Internal Address: 171 97 Stockholm
Street Address:
City: Stockholm State: Sweden Zip:Additional name(s) & address(es) attached? ☐
Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of
the application is:

A. Patent Application No.(s)

B. Patent No.(s)
4,757,057Additional numbers attached? ☐ Yes ☒ No5. Name and address of party to whom
correspondence concerning document
should be mailed:Name: Pollock, Vande Sande & PriddyInternal Address: P.O. Box
19088
Street Address: 1990 M Street,
N.W. Suite 800
City: Washington State: D.C. Zip:
200366. Total number of applications and
patents involved 17. Total fee (37 CFR 3.41).....\$40
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To the best of my knowledge and belief, the foregoing information is true and correct
and any attached copy is a true copy of the original document.Burton A. Amernick
Name of Person Signing

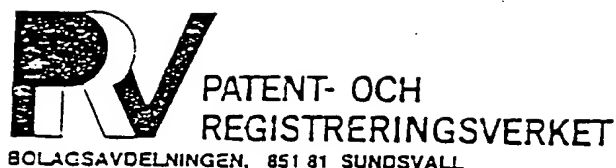
Signature

June 25, 1997
DateTotal number of pages comprising cover sheet: 5

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CERTIFICATE OF REGISTRATION

Registration number: 556131-9608
 Date of registration: 1969-12-30
 Company name: Pharmacia Aktiebolag
 Address:
 Registered office: 171 97 STOCKHOLM
 Stockholm
 Share capital: SEK 6.340.955.550



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 490414-1415 Ingelmark, Lars Rolf Bosson, Skälleredsvägen 94,



PATENT- OCH
REGISTRERINGSVERKET

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CERTIFICATE OF REGISTRATION

Registration number: 556131-9608
Date of registration: 1969-12-30
Company name: Pharmacia Aktiebolag
Address: 171 97 STOCKHOLM
Registered office: Stockholm
Share capital: SEK 6.340.955.550

439 32 ONSALA
411009-3913 Jeppsson, Lars Ingvar, Tussilagovägen 12,
541 41 SKÖVDE
541123-0054 Lidgård, Mats Olof Magnus, Djursholmsvägen 95,
183 51 TÄBY
470417-9193 Åström, Per Håkan Albin, Edsviksvägen 69 B,
191 43 SOLLENTUNA

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116 24 STOCKHOLM
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133 00 SALTSJÖBADEN

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162 40 VÄLLINGBY
451120-7732 Holm, Peter Axel Anders, Vinbärsvägen 16,
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In addition to the Board of Directors,
Ekberg, Jan Erland

alone,

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Blomberg, Jan Fredrik
Blomberg, Nils Carl-Johan
Borg, Rune Helmer
Carlson, Hans William
Ingelmark, Lars Rolf Bosson
Jeppsson, Lars Ingvar
Lidgård, Mats Olof Magnus
Åström, Per Håkan Albin

or Gyll, John Sören
Lund, Olof Gösta

jointly, are entitled to sign on behalf of the company.

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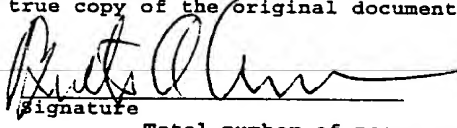
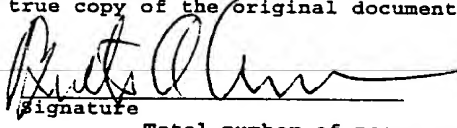
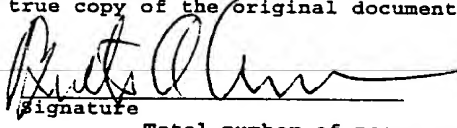
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Please record the attached original documents or copy thereof.

1. Name of conveying party(ies) Pharmacia Aktiebolag Additional name(s) of conveying party(ies) attached? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		2. Name and address of receiving party(ies): Name: <u>Pharmacia & Upjohn Aktiebolag</u> Internal Address: <u>S-112 87 Stockholm</u> Street Address: City: <u>Stockholm</u> State: <u>Sweden</u> Zip:								
3. Nature of conveyance: <input type="checkbox"/> Assignment <input checked="" type="checkbox"/> Merger <input type="checkbox"/> Security Agreement <input type="checkbox"/> Change of name <input type="checkbox"/> Other Execution Date: <u>August 13, 1996</u>		Additional name(s) & address(es) attached? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No								
4. Application number(s) or patent number(s): If this document is being filed together with a new application, the execution date of the application is: <table border="1"><tr><td>A. Patent Application No.(s)</td><td>B. Patent No.(s) <u>4,757,057</u></td></tr></table> Additional numbers attached? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No				A. Patent Application No.(s)	B. Patent No.(s) <u>4,757,057</u>					
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5. Name and address of party to whom correspondence concerning document should be mailed: Name: <u>Pollock, Vande Sande & Priddy</u> Internal Address: <u>P.O. Box 19088</u> Street Address: <u>1990 M Street, N.W. Suite 800</u> City: <u>Washington</u> State: <u>D.C.</u> Zip: <u>20036</u>		6. Total number of applications and patents involved <input type="checkbox"/> 7. Total fee (37 CFR 3.41).....\$40 <input checked="" type="checkbox"/> Enclosed <input type="checkbox"/> Authorized to be charged to deposit account 8. Deposit Account No: (Attach duplicate copy of this page if paying by deposit account)								
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9. Statement and signature. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document. <table border="0"><tr><td><u>Burton A. Amernick</u> Name of Person Signing</td><td> Signature</td><td><u>June 26, 1997</u> Date</td><td rowspan="2">Total number of pages comprising cover sheet: <u>4</u></td></tr><tr><td colspan="3"></td></tr></table>				<u>Burton A. Amernick</u> Name of Person Signing	 Signature	<u>June 26, 1997</u> Date	Total number of pages comprising cover sheet: <u>4</u>			
<u>Burton A. Amernick</u> Name of Person Signing	 Signature	<u>June 26, 1997</u> Date	Total number of pages comprising cover sheet: <u>4</u>							
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PATENT- OCH REGISTRERINGSVERKET
Bolagsavdelningen
SWEDEN

CERTIFICATE OF REGISTRATION

Registration number: 556131-9608
Date of registration: 1969-12-30
Company name: Pharmacia & Upjohn Aktiebolag
Address:
Registered office: 112 87 STOCKHOLM
Stockholm
Share capital: SEK 6.393.802.825

**BOARD OF DIRECTORS:**

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181 46 LIDINGÖ
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756 52 UPPSALA
491010-1817 Jenadri, Joseph, (A), Imatragatan 164, 164 78 KISTA
411009-3913 Jeppsson, Lars Ingvar, Tussilagovägen 12,
541 41 SKÖVDE
541123-0054 Lidgard, Mats Olof Magnus, Djursholmsvägen 95,
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MANAGING DIRECTOR:

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600301-2736 Arvidsson, Nils Göran, Malungsvägen 29, 167 75 BROMMA
510119-3356 Carlson, Hans William, Lärkvägen 9, 183 51 TÄBY
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182 63 DJURSHOLM
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480521-2851 Johnsson, Jörgen Jan-Krister, Tjärögatan 108,
257 33 RYDEBÄCK
560312-2317 Lundberg, Magnus Åke, Gullvivevägen 5, 756 55 UPPSALA
450703-7135 Pettersson, Nils Göran, Östermalmsgatan 68 A,
114 50 STOCKHOLM

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Bolagsavdelningen
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Address:
Registered office: 112 87 STOCKHOLM
Stockholm
Share capital: SEK 6.393.802.825

530920-0250 Pollare, Bror Thomas, (U), Svärdsjövägen 6,
167 57 BROMMA
440211-4674 Ring, Sven Göran, Lagmansvägen 11, 181 63 LIDINGÖ
410109-8251 Sievertsson, Hans Uno, Rystavägen 5, 183 46 TÄBY
470806-1074 Würtz, Jan Sven Erik, Fäbodgränd 6, 175 45 JÄRFÄLLA

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165 72 HÄSSELBY
460515-0657 Tidström, Hans Göran, Knut Wallenbergs väg 39,
133 00 SALTSJÖBADEN

DEPUTY AUDITORS:

571022-1101 Blom, Eva Mari, Odalvägen 6, 740 22 BÄLINGE
470411-7219 Danielsson, Åke Nils Gunnar, Neptunistigen 70,
162 40 VÄLLINGBY

SIGNATORY POWER:

In addition to the Board of Directors,
any two jointly of

Blomberg, Nils Carl-Johan
Jeppsson, Lars Ingvar
Lidgard, Mats Olof Magnus
Ingelmark, Lars Rolf Bosson
Arvidsson, Nils Göran
Carlson, Hans William
Gatenbeck, Lars Ernst Vilhelm
Hudson, Leslie
Johnsson, Jörgen Jan-Krister
Lundberg, Magnus Åke
Pettersson, Nils Göran
Pollare, Bror Thomas
Ring, Sven Göran
Sievertsson, Hans Uno
Würtz, Jan Sven Erik

are entitled to sign on behalf of the company.

CONTD.

PRV

PATENT- OCH REGISTRERINGSVERKET

Bolagsavdelningen

SWEDEN

CERTIFICATE OF REGISTRATION

Registration number: 556131-9608
Date of registration: 1969-12-30
Company name: Pharmacia & Upjohn Aktiebolag
Address:

Registered office: 112 87 STOCKHOLM
Stockholm
Share capital: SEK 6.393.802.825

Pursuant to Section 8, sub-section 12, of the Companies Act, the Managing Director, in his normal business activities, is also entitled to sign on behalf of the company.

FINANCIAL YEAR:

Registered financial year: 0101-1231

Latest annual report submitted covers financial period 950101-951231

DATE OF REGISTRATION OF CURRENT AND PREVIOUS COMPANY NAMES:

1996-07-01 Pharmacia & Upjohn Aktiebolag

1993-11-17 Pharmacia Aktiebolag

1984-12-27 Procordia Aktiebolag

1969-12-30 Statsföretag Aktiebolag

SUNDSVALL 1996-08-13

Ex officio



GUNN LAHTI



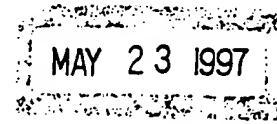
- (A) = employee representative
(U) = person resident outside EEA
(E) = person resident outside Sweden but within EEA



NDA 20-227

CONFIDENTIALFood and Drug Administration
Rockville MD 20857

Wyeth-Ayerst Laboratories
Attention: Roy J. Baranello, Jr.
P.O. Box 8299
Philadelphia, PA 19101-8299



Dear Mr. Baranello:



Please refer to your new drug application dated December 16, 1992, received on December 16, 1992 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Normiflo® (ardeparin sodium) Injection.

We acknowledge receipt of your submissions dated December 20 and 23, 1996, and January 7 and May 1, 1997, in response to our November 13, 1996 approvable letter. The current user fee goal date for this application is November 2, 1997.

This new drug application provides for prevention of deep venous thrombosis which may lead to pulmonary embolism following knee replacement surgery using ardeparin sodium injection produced with drug substance manufactured by Wyeth-Ayerst.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated May 1, 1997 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

1. In the CLINICAL PHARMACOLOGY section, "Pharmacokinetics/Pharmacodynamics" subsection, the paragraph entitled "*Population Pharmacokinetic Profile*", revise the first sentence to read: "In two large-scale clinical trials, 934 patients undergoing hip or knee replacement surgery were administered either 50 anti-Xa U/kg every 12h or 90 anti-Xa U/kg once a day subcutaneously for up to 14 days, and plasma samples were collected before each morning dose and 6 hours later."
2. In the ADVERSE REACTIONS section, in the tables entitled "Hemorrhagic Events Occurring in 2% or More of Patients Treated with Normiflo 50 Anti-Xa U/kg Every 12 Hours in Controlled Studies: % of Patients" and "Nonhemorrhagic Adverse Events Occurring in 5% or More of Patients Treated with Normiflo 50 Anti-Xa U/kg Every 12 Hours in Controlled Studies: % of Patients", revise the column heading "Drug Related" to "Attributed by Investigator to Drug".

CONFIDENTIAL

NDA 20-227

Page 2

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-227. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

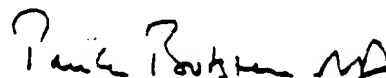
Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Karen Oliver, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Paula Botstein MD".

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

United States Patent [19]

Fussi et al.

[11] Patent Number: 4,757,057

[45] Date of Patent: Jul. 12, 1988

[54] OLIGO-HETEROPOLYSACCHARIDES
HAVING A HEPARIN-LIKE ACTIVITY
METHOD FOR THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS
BASED THEREON

[75] Inventors: Fernando Fussi, Lesmo; Gianfranco
Fedeli, Milan, both of Italy

[73] Assignee: Hepar Chimie S.A., Switzerland

[21] Appl. No.: 816,838

[22] Filed: Jan. 7, 1986

Related U.S. Application Data

[63] Continuation of Ser. No. 347,026, Feb. 8, 1982, abandoned, which is a continuation of Ser. No. 931,295, Aug. 4, 1978, abandoned.

[30] Foreign Application Priority Data

Aug. 9, 1977 [IT] Italy 26608 A/77

[51] Int. CL⁴ A61K 31/725

[52] U.S. Cl. 514/56; 514/54

[58] Field of Search 514/56

[56] References Cited

U.S. PATENT DOCUMENTS

2,832,766 4/1952 Wolfrom 260/211
3,585,184 12/1967 Wolfrom et al. 260/209

FOREIGN PATENT DOCUMENTS

968752 3/1958 Fed. Rep. of Germany .
1032731 6/1958 Fed. Rep. of Germany .
674607 6/1952 United Kingdom 424/183

OTHER PUBLICATIONS

Hladovec et al—*Experientia*, vol. XIII/5, May 15, 1957, pp. 190 & 191.

Thrombosis Research, vol. 9, pp. 575–583, 1976; vol. 12, 257–271 (1978); vol. 12, pp. 27–36, 1977.

Biochimica et Biophysica Acta, 343 (1974), 324–329.

Proceedings of the Society for Experimental Biology and Medicine, 146, 504–508 (1974).

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Kevin M. Foley

[57]

ABSTRACT

A oligo-heteropolysaccharide is disclosed which is very active against thrombotic syndromes and is prepared starting from depolymerized heparin fractions wherein the active groups, more particularly the sulfuric groups have been reconstituted by reacting a heparin fraction with a mol wt from 2,000 to 5,000 with the sulfotrioxide of a nitrogeous organic base such as pyridine and trimethylamine. The method of preparation is also disclosed.

3 Claims, No Drawings

EXHIBIT

6

ALL-STATE® INTERNATIONAL

OLIGO-HETEROPOLYSACCHARIDES HAVING A HEPARIN-LIKE ACTIVITY METHOD FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS BASED THEREON

This is a continuation application of Ser. No. 347,026 filed on Feb. 8, 1982, now abandoned, which is a continuation of application Ser. No. 931,295 filed Aug. 4, 1978, now abandoned.

This invention relates to a hetero-polysaccharide which is susceptible of finding a therapeutical application, in general, in the prevention of thrombotic phenomena.

Another object of the present invention is to provide a method for the preparation of such a hetero-polysaccharide.

Yet another object of the present invention is to indicate therapeutic uses and pharmaceutical compositions which contain as the active ingredient the oligo-heteropolysaccharide of the present invention.

Thrombosis is one of the most frequent factors of casualties and ailments, these latter often showing a permanent invalidity pattern in the field of the cardiovascular ailments.

The general term "thrombosis" may include conditions displaying an exalted tendency to blood-clotting, the origins of which can be attributed to:

"hazardous factors" originating a thrombogenic state, such as tobacco smoke, the stresses, the prolonged use of contraceptives of the progestogen type and others,

hereditary factors, such as the lack of blood-clotting-inhibiting factors, more particularly antithrombin III,

causative factors of various origin, sometimes not yet elucidated, such as modification of the platelet adhesiveness and others,

factors deriving from a temporary slowing down of the blood circulation such as is experienced subsequently to surgical operations under narcosis.

The pathological after-effects consequential to a "thrombogenic" condition as caused by one or more of the factors enumerated above can be:

pulmonary, cerebral, coronaric and other thrombo-embolism,

thrombosis of the deep-lying veins,
thromboplebites, varicose syndromes,
diffuse scattering of intravascular microthrombi.

Before so imposing a number of phenomena, it is possible, at present, to have recourse to two approaches:

1. The use of thrombolytic agents,
2. The preventative therapy of thrombogenic conditions and their after-effects. On account of the seriousness and the rapidity of the possible evolution of thromboses, it is apparent that, of the two approaches, the second one is to be preferred by far.

In order to face the thrombosis problem from the preventative angle, two classes of medicaments are now available, viz. the oral anticoagulants such as coumarin and its derivatives and heparin.

Oral anticoagulants such as coumarin and its derivatives act at the liver level and block the two blood-clotting factors proconvertin and prothrombin, but give rise to cumulative phenomena and thus lends themselves poorly to a prolonged treatment and, moreover, even though they are anticoagulants, have but a poor anti-thrombotic activity since they have no action on other

blood-clotting factors which are closely involved in the thrombogenesis, the Xa factor and the platelet factors above all.

Heparin, under this respect, yet offers advantages in that it acts upon the several plasmatic factors of blood-clotting and especially upon thrombin, the factor Xa and also on the XII factor, the XI factor and the IX factor in addition to the platelet factor called PF4. All of these actions are to be attributed to the specific ability by thrombin to unblock the inhibitor of the blood-clotting factors enumerated above, said inhibitor being present in the plasma. This inhibitor is the antithrombin III and requires, just as a co-factor to unfold its action, the presence of heparin.

Regrettably enough, heparin has two defects: in the first place, it is active only parenterally and its effect lasts for 8-12 hours as a maximum, so that it is difficult to bring about a prolonged prophylaxis, for which 2 heparin shots daily are required. In the second place, heparin has not only an antithrombotic effect but also an anti-blood-clotting action as a whole. Now, if this second effect is an asset in certain instances, in other cases the haemorrhage hazard, if the therapy is not adapted to the individual patient, becomes a serious trouble even if the prophylaxis of thrombosis offers advantages beyond any doubt.

Low mol. wt. heparin fractions are found in two cases:

(a) when depolymerizing heparin which chemical or enzymic methods (cfr. A. Horner, in "HEPARIN", Kakkar, Thomas, 1976 and Perhin and cow., Carb. Res., 18, 185 (1971)).

(b) in the mother liquors of the processes for extracting heparin for therapeutical use.

Such fractions, having a mol wt of 5,000 and containing variable amounts of sulfuric groups, generally less numerous than in heparin, have not found any useful therapeutic application heretofore.

It has now been found that such fractions, should they contain the sulfuric groups in the quantities and the positions which are characteristic of the heparin molecule, have pharmacological properties which are akin to those of heparin and therapeutical properties even improved over those of heparin. More particularly, it has been ascertained that:

(i) oligopolysaccharide fractions coming from the depolymerization of heparin, or corresponding to depolymerized heparins having a mol wt comprised between 2,000 and 5,000 have biopharmacological properties which are improved over those of heparin, providing that they are appropriately treated so as to rebuild the active groups;

(ii) differently from heparin as such, the thus treated fractions are active also by the oral route;

(iii) the fractions thus treated are more readily absorbed by the skin than is heparin;

(iv) more particularly, depolymerized and reconstituted heparins are endowed with a ratio of the anti-thrombotic activity to the anti-blood-clotting activity which is favourable over that of the commercial heparin.

The method according to the present invention can be summarized as follows: the starting material is selected from among the heparin oligomers having a mol wt comprised between 2,000 and 5,000 and the low mol wt fractions and is treated with an equal amount by wt of sulfotrioxides of nitrogenous organic bases such as

pyridine sulfotrioxide, trimethylamine sulfotrioxide and other in an alkaline environment.

On completion of the reaction, the product is precipitated with water-miscible solvents such as ethanol, acetone and others and is taken up in an aqueous solution and purified by flowing through ion-exchange resins or molecular sieves.

From the solution the product is obtained by precipitation with water-miscible solvents or by freeze-drying.

The product thus obtained has the following properties:

Identification:

an ivory-colored powder which is slightly hygroscopic, aqueous solution which is clear or slightly opalescent, pH of the 5% aqueous solution: 7 to 8,

identification metachromatic reaction: 1 ml of a 2% solution of the product, added to 1 ml of a 0.0025% toluidine blue solution acidified with 0.1 ml of 1-N hydrochloric acid discharges the color from blue to reddish-blue,

specific rotatory power of the aqueous solution $[\alpha]_D^{20} = +40^\circ / +50^\circ$,

electrophoresis on cellulose acetate pyridine/acetic acid/water-1/10/229, pH 4.5 and development with toluidine blue)=a single band having an anodic mobility $U = 2.1 \cdot 10^{-4} \text{ cm}^2 \text{ v}^{-1} \text{ sec}^{-1}$.

Other chemical specifications of the invention are:

Average mol wt (determined with the Somogy method in comparison with commercial heparin): between 2,600 and 5,500 daltons.

Hexosamines after hydrolysis (reaction with carbazol): $31 \pm 4\%$,

Organic SO_4^{--} after hydrolysis (titration with naphtharsonic acid): $30 \pm 4\%$,

Molar ratio uronic acids/hexosamines/ $\text{SO}_4^{--} = 1/1/2$.

The following Examples show particularly the method of preparation of the products according to the invention without any limitation.

EXAMPLE 1

500 g of an oligopolysaccharide having the following fundamental analytical characteristics:

pH of the 5% solution: 5.8

Organic SO_4^{--} : 13.6%

rotatory power $[\alpha]_D^{20} = +48^\circ$

mol wt (determined with the Somogy method in comparison with commercial heparin) = $4,850 \pm 300$ daltons,

Hexosamines: 33.5%

Uronic acids: 31.8%

Anticoagulant activity: virtually nil, have been admixed in powder with 500 g of Pyridine sulfotrioxide and 500 g of anh. sodium carbonate.

The mixture has been slurried in 10 liters of distilled water and kept stirred for 2 hrs. at room temperature.

Once that time has elapsed, the liquid has been treated with 20 liters of methanol. A white precipitate has been formed, which, separated by centrifuging, has been redissolved in 5 liters of distilled water and passed through a column (diameter 16 cm. height 110 cm) containing 20 liters of Dowex Retardion 11 A 8.

The eluate has been adjusted to a pH of 6 with 20% sodium hydroxide and treated with 2 volumes of methanol. Upon decantation, the white precipitate has been dehydrated with methanol and dried in a vacuum at 40°C . Yield: 365 g.

The product has displayed the following properties upon analysis:

pH of the 5% solution: 6.5

Organic SO_4^{--} : 31%

rotatory power: $[\alpha]_D^{20} = +47^\circ$

mol wt (determined with the Somogy method in comparison with commercial heparin: $5,300 \pm 350$ daltons)

hexosamines: 28.5%

uronic acids: 30%

anticoagulant activity: 36 U/gm (USP)

EXAMPLE 2

250 g of trimethylamine sulfotrioxide and 250 g of anh. sodium carbonate have been admixed, in powder form, with 250 g of an oligopolysaccharide having the following fundamental analytical properties:

pH of the 5% aqueous solution: 6.4

mol wt (determined with the Somogy method in comparison with commercial heparin: $3,400 \pm 400$ daltons)

Organic SO_4^{--} : 11.8%

Hexosamines: 34.2%

Uronic acids: 36%

Anticoagulant activity (USP): 0.5 U/mg

The mixture has been dispersed in 5 liters of dist. water and stirred 12 hours at 55°C . After this time has elapsed, the solution has been passed through a bed of 10 liters of Dowex Retardion 11 A 8. The eluate has been adjusted to a pH of 6 with 20% sodium hydroxide and treated with three volumes of acetone. A white precipitate has been formed which, after decantation, has been dehydrated with acetone and dried in a vacuum at 40°C . Yield: 165 g.

The product has shown the following analytical properties:

pH of the 5% aqueous solution: 7.1%

Rotatory power: $[\alpha]_D^{20} = +42^\circ$

mol wt (determined with the Somogy method in comparison with commercial heparin: $3,900 \pm 280$ daltons)

Organic SO_4^{--} : 28.5%

Hexosamines: 29%

Uronic acids: 30%

Anticoagulant activity: 17 U/mg (USP)

The product obtained with the method described above has been subjected to assays to ascertain its pharmacobiological properties and its activity.

Toxicological tests:

No toxic effects when administered orally to rats, mice, rabbits and Guinea pigs up to a dose of 1,000 mg/kg b.w.

LD₅₀ i.p. (mice) more than 3,000 mg/kg b.w.: LD₅₀

i.v. (mice): more than 1,000 mg/kg b.w.

LD₅₀ i.p. (rats) about 2,000 mg/kg b.w. LD₅₀ i.v. (rats) 354 mg/kg b.w.

Clarifying activity test:

The product lowers the serum levels of the triglycerides considerably in animals affected by experimental hyperlipaemia from Triton.

Anticoagulant activity:

USP equal to, or more than 50 U/mg

Kaolin-Cephalin clotting time test (KCCT): 7-19

Ratio of antithrombotic activity to anticoagulant activity in vitro (Yin's/KCCT): 2.5.

In vivo (dogs) antithrombotic and anticoagulant activity.

The product, administered intravenously (i.v.) (25 IU/kg) and orally (300-1500 U/kg) extends the thrombin time and the KCCT, and protects against thrombosis as induced by thromboplastines.

In vivo (rabbits) antithrombotic activity.

The product administered intravenously at the dose of 20 Anti Xa U/kg protects from thrombine-induced thrombosis.

Thus, the following predictable therapeutical uses are suggested, either orally or parenterally:

prevention of post-operative thromboembolisms

prevention of thrombotic seizures consequent to a thrombogenic conditions such as for example that

which occurs in fertile women when treated for a long time with oral contraceptives of progestogenic type

prevention of venous thromboses

prevention of hypercoagulability states

correction of the hyperdislipaemic states (hyperdislipoproteinaemias).

We claim:

1. A method of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity comprising administering to a mammal in need of treatment for thrombosis, an oligoheteropolysaccharide comprising depolymerized heparin containing sulfate groups in the quantity and in the positions characteristic of heparin wherein said oligoheteropolysaccharide has the following physico chemical properties:

(A) average molecular weight (determined with the Somogy method in comparison with commercial heparin) from 2600 to 5500 daltons;

(B) hexosamines after hydrolysis (reaction with p-dimethyl-amino benzaldehyde): $28\% \pm 2\%$;

(C) uronic acids after hydrolysis (reaction with carbazol): $31\% \pm 4\%$;

(D) organic SO_4^- after hydrolysis (titration with naphtharsone): $30\% \pm 4\%$;

(E) molar ratios of uronic acids/hexosamines/ $\text{SO}_4^- = 1/1/2$;

(F) specific rotatory power of the aqueous solution $[\alpha]_D^{20} = +40^\circ - +50^\circ$;

(G) electrophoresis on cellulose acetate (pyridine/acetic acid/water (1:10:299)) pH 4.5 and development with toluidine blue=a single band with anodic mobility $U = 2.1 \times 10^{-4} \text{ cm}^2 \text{ v}^{-1} \text{ sec}^{-1}$;

(H) powder of ivory color, amorphous and slightly hygroscopic;

(I) aqueous solution clear or slightly opalescent; and

(J) pH of 5% aqueous solution: 7-8.

2. A method of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity comprising administering to a mammal in need of treatment for thrombosis an oligoheteropolysaccharide comprising depolymerized heparin having an average molecular weight of about 2600 to about 5500 daltons determined by the Somogy method in comparison with commercial heparin and having sulfate groups in the quantity and in the positions characteristic of heparin, which oligoheteropolysaccharide displays greater antithrombotic activity than anticoagulant activity.

3. A method of increasing the antithrombotic activity of mammalian blood relative to the anticoagulant activity comprising administering to a mammal an effective amount of a therapeutical composition, for the prevention of thrombosis, characterized in that it contains as the active ingredient the oligoheteropolysaccharide as described in claims 1 or 2.

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REGULATORY CHRONOLOGY FOR

NORMIFLO (ARDEPARIN SODIUM) INJECTION



September 21, 1987	IND submitted to FDA.
September 28, 1987	Letter from FDA assigning IND No. 30,639 for RD Heparin Sodium Injection.
November 5, 1987	Letter from FDA with recommendations and requests concerning inclusion/exclusion criteria, coagulation tests, pharmacokinetic evaluations, immunological evaluations, and cross-over scheme of the clinical protocol submitted on 9/21/87.
November 30, 1987	Submission of additional phase 1 protocol and investigators.
December 2, 1987	Submission of Amendments I and II to phase 1 protocol.
December 22, 1987	Letter to FDA with a response to recommendations and requests made in FDA letter of 11/5/87.
December 29, 1987	Submission of additional phase 1 protocol and investigators.
April 7, 1988	Letter to FDA discontinuing a phase 1 protocol.
May 11, 1988	Submission of two phase 2 protocols and investigators.
June 27, 1988	Letter from FDA with comments on 5/11/88 submission.
August 11, 1988	Letter to FDA with a response to the comments made in FDA letter of 6/27/88.
August 19, 1988	Submission of Amendment I to a phase 2 protocol.
September 26, 1988	Letter to FDA requesting a meeting to discuss clinical development and pharmacology and toxicology studies needed to support the clinical trials.
October 6, 1988	Submission of Amendment II to a phase 2 protocol.
November 18, 1988	Submission of IND annual progress report.
December 5, 1988	Letter to FDA containing a response to FDA's request for information from a 10/14/88 telephone conversation concerning a phase 2 protocol.
December 22, 1988	Letter from FDA with recommendations and requests concerning the Chemistry, Manufacturing and Controls section of the original submission.
December 23, 1988	Submission of two phase 2 protocols and investigators.
December 30, 1988	Submission of a revised phase 2 protocol.

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

January 4, 1989	Submission of a phase 1 protocol and investigators.
January 19, 1989	Letter to FDA confirming a meeting to be held on 1/27/89.
February 10, 1989	Submission of Amendment I to two phase 2 protocols.
March 1, 1989	Letter from FDA with recommendations and requests concerning a phase 2 protocol.
March 1, 1989	Letter from FDA with recommendations and requests concerning a phase 1 protocol.
March 7, 1989	Submission of Amendment III to a phase 2 protocol.
April 6, 1989	Letter from FDA with requests concerning a phase 1 protocol.
April 6, 1989	Letter from FDA with recommendations concerning two phase 2 protocols.
April 7, 1989	Letter to FDA containing a memorandum of the 1/27/89 meeting concerning toxicological and clinical development.
April 21, 1989	Letter from FDA summarizing the meeting held on 1/27/89.
April 26, 1989	Letter to FDA with a response to comments made in FDA letter of 3/1/89.
May 4, 1989	Submission of three GMRs summarizing the data pertaining to phase 1 protocols.
May 19, 1989	Submission of Amendment II to a phase 1 protocol.
May 25, 1989	Submission of response to recommendations made in FDA letter of 4/6/89.
June 6, 1989	Submission of five GTRs pertaining to pharmacology and toxicology.
July 7, 1989	Submission of two phase 3 protocols.
July 7, 1989	Submission of GTR No. 17170 in response to a request made in FDA letter of 3/1/89.
August 1, 1989	Submission of Amendment I to a phase 2 protocol.
August 9, 1989	Letter to FDA with a response to comments made in FDA letter of 4/21/89.
August 9, 1989	Submission of nine GTRs pertaining to pharmacology and toxicology.
August 25, 1989	Submission of an updated list of manufacturing sites.
September 18, 1989	Submission of IND annual report.

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

September 28, 1989	Submission of a phase 3 protocol.
November 6, 1989	Submission of two GTRs pertaining to pharmacology and toxicology.
December 6, 1989	Submission of an IND Safety Report.
January 4, 1990	Letter from FDA with recommendations and requests for additional information concerning GTR No. 17169 submitted on 8/9/89.
January 10, 1990	Submission of an IND Safety Report.
January 12, 1990	Submission of a follow-up to an IND Safety Report.
January 23, 1990	Submission of Amendment I to a phase 3 protocol.
January 31, 1990	Submission of Amendment II to a phase 3 protocol.
February 15, 1990	Submission of three phase 3 protocols and investigators.
March 9, 1990	Submission of amendments to three phase 3 protocols.
March 27, 1990	Letter to FDA with a response to the request for additional information made in FDA letter of 1/4/90 concerning the information amendment submitted on 8/9/89.
April 4, 1990	Letter to FDA with a response to the recommendations and requests described in FDA letter of 12/22/88 concerning manufacturing and control issues.
April 12, 1990	Letter from FDA with comments concerning the amendments submitted on 3/9/90.
April 23, 1990	Submission of a phase 1 protocol and investigators.
April 24, 1990	Submission of nine GTRs pertaining to drug metabolism, pharmacology and toxicology.
May 4, 1990	Submission of a phase 1 protocol and investigators.
May 14, 1990	Letter to FDA requesting a teleconference pertaining to a clinical study.
May 22, 1990	Letter from FDA with recommendations and requests pertaining to Amendment I of GTR No. 17169.
June 13, 1990	Letter to FDA with comments pertaining to a teleconference held on 5/22/90.
June 18, 1990	Submission of an information amendment for changes in the chemistry, manufacturing and control data.

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

June 19, 1990	Submission of Amendment I to a phase 3 protocol.
July 12, 1990	Letter to FDA withdrawing the amendments submitted on 3/9/90.
July 26, 1990	Letter to FDA requesting review and concurrence of the design of a phase 3 protocol.
August 1 st , 1990	Submission of response to FDA letter of 3/1/89.
August 21, 1990	Submission of the minutes from a 6/27/90 meeting with FDA.
August 24, 1990	Letter from FDA with recommendations and requests concerning a phase 3 protocol.
August 28, 1990	Submission of Amendment I to a phase 1 protocol.
August 29, 1990	Letter from FDA with questions, recommendations and requests concerning the chemistry amendment submitted on 6/18/90.
September 13, 1990	Letter from FDA with requests for additional information concerning the toxicology report submitted on 4/24/90.
September 19, 1990	Submission of chemistry, manufacturing and controls data in response to FDA letter of 12/22/88 and W-A letter of 4/4/90.
September 21, 1990	Letter to FDA with a response to recommendations and requests described in FDA letter of 8/24/90.
September 28, 1990	Letter to FDA requesting an End-of-Phase II meeting.
October 11, 1990	Letter to FDA with a response to the recommendations and requests described in FDA letter of 5/22/90.
October 26, 1990	Letter to FDA confirming the date of an end of Phase II meeting.
October 30, 1990	Submission of IND annual report.
November 19, 1990	Submission of official copy of a phase 3 protocol and investigators.
December 17, 1990	Submission of minutes of the End-of -Phase II meeting held on 11/20/90.
December 20, 1990	Submission of Amendment III to a phase 2 protocol.
February 11, 1991	Letter from FDA with requests for information pertaining to manufacturing and control issues submitted on 4/4/90 and 9/19/90.

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

February 27, 1991	Letter to FDA with a response to the recommendations and requests described in FDA letters of 8/29/90 and 2/11/91 concerning the chemistry, manufacturing and control amendment submitted 6/18/90.
March 12, 1991	Letter to FDA with a request for a pre-NDA meeting.
March 26, 1991	Letter to FDA with copies of pre-NDA package.
April 30, 1991	Letter to FDA confirming date of pre-NDA meeting and list of attendees.
May 7, 1991	Letter from FDA with a summary of the End-of-Phase II meeting held on 11/11/90.
May 14, 1991	Submission of Amendment I to a phase 3 protocol.
May 29, 1991	Letter to FDA with a response to recommendations and requests described in FDA letter of 2/11/91 concerning manufacturing and controls.
June 5, 1991	Letter to FDA with minutes of pre-NDA meeting held 5/9/91.
June 26, 1991	Submission of a report concerning absolute and relative bioavailability in response to FDA's comments made during the pre-NDA meeting.
July 23, 1991	Letter from FDA with a summary of the pre-NDA meeting held 5/9/91.
September 4, 1991	Letter from FDA with a request for additional information concerning the submission of 6/26/91.
September 5, 1991	Letter to FDA with a request for an additional pre-NDA meeting.
September 9, 1991	Submission of thirteen GTRs pertaining to pharmacology, toxicology and preclinical ADME.
September 11, 1991	Letter to FDA requesting a review of the revised criteria on the proposed populations for efficacy analysis of pivotal protocols.
September 30, 1991	Letter to FDA with a response to a request for additional information described in FDA letter of 9/4/91.
October 15, 1991	Letter to FDA confirming second pre-NDA meeting and list of attendees.
October 17, 1991	Letter from FDA with a request for additional clarification of the information presented in the submission of 9/11/91.
November 6, 1991	Letter to FDA with the minutes of the second pre-NDA meeting held on 10/21/91.

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

November 13, 1991	Letter from FDA with a recommendation for an additional study in response to the information submitted on 9/30/91.
December 5, 1991	Letter to FDA with a response to FDA letter of 11/13/91.
December 17, 1991	Letter to FDA with the minutes from the 12/10/91 meeting and submission of additional items for review.
December 20, 1991	Submission of IND annual report.
January 21, 1992	Submission to FDA of Amendment IV to a phase 2 protocol.
January 27, 1992	Letter to FDA with a response to a request for additional information described in FDA letter of 10/17/91 concerning pivotal protocols.
March 4, 1992	Letter from FDA with concluding comments concerning the submission of 10/11/90.
April 6, 1992	Letter to FDA with information requested from FDA during a 3/23/92 teleconference pertaining to a phase 1 protocol.
July 24, 1992	Submission of additional information concerning the status of a phase 3 protocol, a proposed interim analysis, and an amendment to the protocol.
August 5, 1992	Submission of a revised Investigational Drug Brochure.
August 12, 1992	Submission of Amendment V to a phase 2 protocol.
September 10, 1992	Letter from FDA with recommendations and requests concerning the proposed interim analysis submitted 7/24/92.
October 13, 1992	Submission of Amendment IV to a phase 2 protocol.
October 20, 1992	Letter from FDA with recommendations and requests concerning the revised Investigator Drug Brochure submitted on August 5, 1992.
October 28, 1992	Submission of Amendment VII to a phase 2 protocol.
November 5, 1992	Submission of a phase 3 protocol, investigators, and supportive chemistry, manufacturing and controls information.
December 8, 1992	Letter to FDA with a request for comments on a proposed interim analysis of a phase 3 protocol.
December 8, 1992	Letter to FDA with a response to requests and recommendations made in FDA letter of 9/10/92.

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NORMIFLO (ARDEPARIN SODIUM) INJECTION

December 18, 1992	Submission of IND annual report.
January 29, 1993	Letter from FDA with comments and requests concerning the proposed interim analysis submitted on 12/8/92.
March 24, 1993	Letter to FDA with notification of termination of a phase 3 protocol.
October 22, 1993	Submission of a phase 1 protocol.
November 9, 1993	Submission of IND annual report.
November 18, 1993	Submission of fourteen GTRs pertaining to pharmacology, toxicology and drug metabolism.
December 7, 1993	Submission of Amendment I to a phase 1 protocol.
January 25, 1994	Submission of Amendment I to a phase 3 protocol.
February 14, 1994	Letter from FDA with recommendations concerning the protocol amendment submitted on 1/25/94.
March 21, 1994	Letter to FDA with a response to the recommendation made in FDA letter of 2/14/94.
April 14, 1994	Submission of a phase 3 protocol and investigators.
April 19, 1994	Submission of chemistry, manufacturing and controls amendment in support of two phase 3 protocols.
April 19, 1994	Submission of a phase 3 protocol and investigators.
November 3, 1994	Submission of Amendment I to a phase 3 protocol.
November 11, 1994	Submission of Amendment I to a phase 3 protocol.
December 21, 1994	Submission of IND annual report.
March 24, 1995	Submission of Amendment II to a phase 3 protocol.
July 13, 1995	Submission of Amendment III to a phase 3 protocol.
July 14, 1995	Submission of Amendment II to a phase 3 protocol.
December 20, 1995	Submission of IND Annual Report.
May 31, 1996	Submission of Amendment IV to a phase 3 protocol.
December 13, 1996	Submission of IND Annual Report.

IND No. 30,639

REGULATORY CHRONOLOGY FOR
NORMIFLO (ARDEPARIN SODIUM) INJECTION

215a/vpz
6/25/97

Regulatory Chronology
NDA No. 20-227
Normiflo® (ardeparin sodium) Injection

<u>Date</u>	<u>Subject</u>
02/28/92	Submission of NDA No. 20-227.
04/20/92	Letter from FDA refusing to file the NDA based upon the need for additional information.
04/24/92	Letter to FDA requesting a conference to discuss the FDA letter of 04/20/92.
05/13/92	Letter to FDA containing a description of the planned responses to each of the items in the 04/20/92 letter.
12/16/92	Resubmission of NDA 20-227 which included responses to recommendations and requests conveyed in 04/20/92 letter from FDA.
03/09/93	FDA letter requesting additional information on both response and control variables in order to complete the review of the stability studies.
03/25/93	Letter to FDA containing Master Production Records (MPRs) used for the manufacture of validation batches of drug substance produced by Wyeth-Ayerst at Rouses Point in response to FDA telephone request of 03/04/93.
04/06/93	Letter to FDA containing revisions to the Wyeth-Ayerst environmental assessment.
04/08/93	Letter to FDA containing statistical information for pivotal clinical studies in response to FDA telephone request of 04/02/93.
04/16/93	Letter to FDA containing additional safety analyses for clinical study in response to FDA telephone request of April 15, 1993
04/20/93	Submission to FDA containing additional stability data on drug product and diskettes containing stability information in SAS data files in response to FDA letter of 03/09/93.
04/23/93	Submission to FDA containing five toxicology reports which were requested in 04/20/92 letter from FDA.
05/03/93	Letter from FDA which states that an additional 90 days will be required to complete the review of the application based on the submissions of 04/20/93 and 04/23/93.
05/21/93	Letter to FDA with a revised table of patient outcomes in response to FDA telephone request of 05/20/93.

<u>Date</u>	<u>Subject</u>
06/15/93	Letter from FDA concerning their completed review of the chemistry, manufacturing and controls section of the NDA with requests for additional CMC information.
06/24/93	Submission to FDA of preliminary efficacy and safety analyses for additional clinical study as requested during teleconference with FDA on 05/27/93.
06/25/93	Letter from FDA with specific recommendations and requests for additional information concerning the drug substance MPRs which Wyeth-Ayerst submitted on 03/25/93.
07/09/93	Letter to FDA to provide clarification concerning sites for the testing and release of drug substance and drug product.
07/21/93	Letter to FDA with responses to all requests for information made by FDA in letter dated 04/16/93.
07/23/93	Submission to FDA of additional safety data for clinical study as committed to in the 06/24/93 letter to FDA.
07/30/93	Letter from FDA which states that an additional 60 days will be required to complete the review of the application based on the submission of 07/23/93.
08/18/93	Letter to FDA with responses to all recommendations and requests made by FDA in letter dated 06/25/93.
08/24/93	Letter from FDA requesting that the safety update be prepared and submitted.
08/30/93	Letter from FDA with request for supplemental information on liberation of sulfate in drug product.
09/07/93	Letter to FDA with responses to all recommendations and requests concerning drug substance and drug product made by FDA in letter dated 06/15/93.
10/25/93	Letter to FDA containing the safety update as requested by FDA on 08/24/93.
11/26/93	Action letter from FDA indicating that the NDA is not approvable due to CMC deficiencies.
01/12/94	Letter to FDA with supplemental drug product stability information in response to FDA action letter dated 11/26/93.
01/17/94	Letter to FDA with proposal on the manufacture of bulk drug product as identified in FDA action letter dated 11/26/93.
01/31/94	Letter to FDA with additional CMC related responses to the FDA action letter dated 11/26/93.
02/04/94	Letter from FDA which states that an additional 60 days will be required to complete the review of the application based on the submission of 01/31/94.

<u>Date</u>	<u>Subject</u>
04/15/94	Letter to FDA with responses to telephone questions regarding the Normiflo Injection drug product stability database.
05/20/94	Letter from FDA with additional questions concerning their review of our 01/12/94, 01/31/94, and 04/15/94 amendments regarding chemistry, manufacturing and controls, and stability data.
06/02/94	Letter to FDA Clinical Investigations Branch with safety information on patients enrolled in second clinical study as requested at meeting held with FDA on 01/06/94.
06/03/94	Letter from FDA requesting clarification of sterility questions on our 1/31/94 and 2/3/94 response to FDA's 11/26/93 action letter.
06/14/94	Letter from FDA which states that an additional 90 days will be required to complete the review of the application based on the submission of 06/02/94.
06/23/94	Action letter from FDA indicating that the NDA is not approvable.
06/29/94	Letter to FDA confirming intent to amend the NDA and to respond to the 06/23/94 action letter.
07/25/94	Submission to FDA of additional clinical and CMC information to support NDA in response to the FDA letters of 06/03/94 and 06/23/94.
08/19/94	Letter to FDA with reanalysis of Normiflo [®] Injection stability data in response to FDA letter of 05/20/94.
09/12/94	Letter to FDA home district office with a copy of the 09/12/94 responses to the FDA letter of 05/20/94.
09/13/94	Letter to Philadelphia District FDA office certifying site readiness for pre-approval inspections.
09/20/94	Letter from FDA which states that the response to the 06/23/94 not approvable letter is a major amendment and the new regulatory due date is 12/30/94 and the new due date under the prescription Drug User Fee Act is 03/14/95.
10/25/94	Letter to FDA Clinical Investigations Branch with information concerning the conduct of third clinical study in response to FDA telephone request of 09/19/94.
11/23/94	Letter from FDA with requests concerning the review of the environmental assessments.
12/06/94	Letter to FDA Clinical Investigations Branch with additional information on third clinical study.
12/09/94	Letter from FDA requesting that information be provided on the bioequivalence between drug product used in clinical trials and the proposed market product.

<u>Date</u>	<u>Subject</u>
12/20/94	Letter to FDA requesting a meeting to discuss the documentation needed to support the bioequivalence information requested by FDA on 12/09/94.
01/03/95	Letter to FDA confirming that a meeting will be held with FDA on 01/04/95 to discuss the FDA letter of 12/09/94.
01/25/95	Submission to FDA of minutes from the 01/04/95 meeting concerning the bioequivalence issues identified in FDA letter of 12/09/94.
03/02/95	Submission to FDA of the full study reports for protocols to support bioequivalence as requested at the 01/04/95 meeting.
03/10/95	Letter from FDA which states that the 03/02/95 submission is a major amendment, the user fee clock is extended three months, and the new due date is 06/15/95.
03/10/95	Letter to FDA with the revised Environmental Assessment for the Wyeth-Ayerst sites of drug substance and product manufacture as requested by FDA on 11/23/94.
04/05/95	Letter to FDA with additional clinical information on fourth clinical study in response to FDA telephone request of 03/20/95.
06/12/95	Action letter from FDA indicating that the NDA is not approvable.
06/14/95	Letter from FDA with minutes of the 01/04/95 meeting concerning the bioequivalence issues identified in FDA letter of 12/09/94.
06/21/95	Letter to FDA confirming intent to amend the NDA and to respond to the 06/12/95 action letter.
08/25/95	Letter to FDA with a response to the FDA action letter of 06/12/95 and containing additional information for third clinical study and additional CMC information.
09/06/95	Letter from FDA acknowledging receipt of the 08/25/95 submission and notification that FDA due date is 02/28/96.
12/20/95	Letter to FDA containing the results of a stability study on sulfate liberation during storage in response to FDA letter of 08/30/93.
12/28/95	Letter from FDA containing recommendations and requests for additional CMC information and acknowledgment of receipt of 12/20/95 submission.
01/19/96	Action letter from FDA acknowledging receipt of the 5/30/95 and 8/25/95 submissions and indicating the application is not approvable.
01/29/96	Letter to FDA confirming intent to amend the new drug application in response to FDA not approvable letter of 01/19/96.

<u>Date</u>	<u>Subject</u>
03/21/96	Submission to FDA containing a response to the recommendations and requests made in FDA letter of 12/28/95 concerning the CMC information.
05/16/96	Letter to FDA containing a full response to the FDA action letter of 01/19/96.
05/23/96	Letter from FDA confirming receipt of 05/16/96 submission and notification that the FDA due date is 11/17/96.
09/06/96	Submission to FDA containing a response of additional CMC information requested during an FDA inspection of the Marietta manufacturing facility.
09/16/96	Submission to FDA containing W-A decision to proceed to approval with Normiflo Tubex only and a revised insert in response to FDA telephone conversation of 09/03/96.
10/04/96	Letter to FDA providing confirmation of final revised specifications for drug substance and drug product as agreed upon during FDA teleconference of 10/01/96 and 10/02/96.
10/11/96	Submission to FDA of amendment to the NDA specifications for drug substance and drug product as committed to in letter of 10/04/96.
10/22/96	Submission to FDA of samples of container and carton labels, and a draft report on Tubex label placement as requested during an FDA telephone conversation of 10/22/96.
11/13/96	Receipt of approvable letter from FDA with requests for the final technical report submitted as a draft on 10/22/96, plus revised labels, a revised package insert, and a safety update.
11/22/96	Letter to FDA with notification of intent to amend the application per the requests delineated in the approvable letter of 11/13/96.
12/20/96	Submission to FDA of final technical report of the Tubex label placement plus a revised package insert, and final printed container and carton labels as requested in the approvable letter of 11/13/96.
12/23/96	Submission to FDA of safety information as requested in the approvable letter of 11/13/96.
03/11/97	Telefax to FDA of a draft of specific sections of the revised package insert as per FDA telephone request of 03/04/97.
05/01/97	Submission to FDA of revised package insert.
05/14/97	Letter from FDA dated 05/09/97 acknowledging receipt of revised draft labeling submitted 05/01/97 and noting that the due date is 11/2/97.
05/27/97	Letter from FDA dated 05/23/97 approving NDA No. 20-227.



UNITED STATES DEPARTMENT OF COMMERCE
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000909

CUSHMAN, DARBY AND CUSHMAN
ATTORNEYS AT LAW
1615 L STREET, N. W.
11TH FLOOR
WASHINGTON, DC 20036-5601

DATE MAILED
01/08/92

195053

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

1061-445

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM	ATTY DKT
NBR	NUMBER

1

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

MAINTENANCE FEE STATEMENT
STATUS CODES AND DEFINITIONS

CODE

DEFINITION

IN REGARD TO THE MAINTENANCE FEE PAYMENT(S)

- F160 The maintenance fee has already been paid. A refund of the payment has been scheduled to be sent to the fee address of record.
- F161 The maintenance fee payment will not be accepted because it has been tendered too early. See 37 CFR 1.362. A refund of the payment has been scheduled.
- F162 The maintenance fee payment does not properly identify the patent for which payment is to be made in accordance with 37 CFR 1.366(c). Either the U. S. application serial number or the patent number has been omitted. Both numbers are necessary to ensure proper crediting of the maintenance fee to the desired patent.
- F163 The maintenance fee payment based upon certificate of mailing procedures is untimely, since it is not in compliance with the requirements of 37 CFR 1.8.
- F164 The maintenance fee payment based upon "Express Mail" procedures is untimely since it is not in compliance with the requirements of 37 CFR 1.10.
- F165 The maintenance fee and surcharge payment are not accepted because they have been submitted with the payment of fees for other purposes. See 37 CFR 1.366(e). A refund of the payment has been scheduled.
- F166 The maintenance fee payment is not accepted because it is not immediately negotiable in the United States for the full payment of the required fee. Payment should be made in U. S. specie, Treasury notes, national bank notes, post office money orders or by certified check. See 37 CFR 1.23. The payment is returned herewith.
- F167 The check or deposit account authorization is not accepted because it is unsigned. It is returned here

- F168 The payment received or the balance in the deposit account authorized for payment is insufficient to cover payment of the maintenance fee and surcharge, if any. Any payments accepted have been applied in accordance with the provisions of 37 CFR 1.366(e).
- F169 The payment is in excess of the amount required. A refund has been scheduled.

IN REGARD TO THE STATEMENT OF SMALL ENTITY STATUS

- E180 A signature to the small entity statement is omitted.
- E181 A small entity statement from each joint inventor has not been received.
- E182 A small entity statement from the assignee or licensee has not been received.
- E183 The requirements for filing as an independent inventor have not been met. See 37 CFR 1.9(c).
- E 184 The requirements for filing as a small business concern have not been met. See 37-CFR 1.9(d).
- E185 The requirements for filing as a nonprofit organization have not been met. See 37 CFR 1.9(e).
- E186 The small entity statement was not verified by an oath or a declaration.

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EXHIBIT

9

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[ANKOM]

1996-05-22

Pharmacia AB
Patent Department
S-112 87 Stockholm
Sweden

Besv

Our ref: 301909/OFRCPT

Your ref:

Date: 12 APR 1996

Dear Sir,

OFFICIAL RECEIPT / RENEWAL CERTIFICATE

Country Name:	U.S.A.
Type Name:	Patent
Patent No.:	4757057
Base date:	12 JUL 1988
Proprietor:	HEPAR CHIMIE SA
Client case code:	14400/40
Reference:	0615US
Client no.:	0784025

Annuity:	2
Renewal date:	12 JAN 1996

We enclose the official receipt for payment of the annuity indicated above. This document should be kept in a safe place in case proof of renewal is required at any time. If you would like your official receipts stored by us in future, rather than sent to you, please let us know by signing and returning this letter.

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Yours faithfully,

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REPRESENTATIVE PARTNERS

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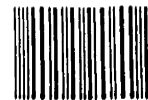
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INSTRUCTION

Please maintain the following
case(s) and send us the official
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28 DEC 1995 17

Case Details

Case No. Annuity
Due date Proprietor

Cost

U.S.A. 4757038 2 US\$1990.00
Patent 12 JAN 1996 NITTO CHEM. IND.
Application No. 052226



US PT 4757038 2

U.S.A. 4757048 2 US\$1990.00
Patent 12 JAN 1996 CALIFORNIA BIOTECHNOLOGY INC.
Application No. 868312



US PT 4757048 2

U.S.A. 4757054 2 US\$1990.00
Patent 12 JAN 1996 KUREHA KAGAKU
Application No. 004308



US PT 4757054 2

U.S.A. 4757057 2 US\$1990.00
Patent 12 JAN 1996 HEPAR CHIMIE SA
Application No. 816838



US PT 4757057 2

U.S.A. 4757060 2 US\$1990.00
Patent 12 JAN 1996 BRISTOL-MYERS CO
Application No. 867882



US PT 4757060 2

U.S.A. 4757073 2 US\$1990.00
Patent 12 JAN 1996 BRISTOL-MYERS CO
Application No. 899695



US PT 4757073 2

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R.B. Thomson, N.R. Jennings, S.J. Colgan, H.L. Milbensch, M.J. Brunner, Fiona M. Crawford, P.A. Bowman, P.J. Walters, P. Coxon, I. Terry, A.J. Coulson.

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT

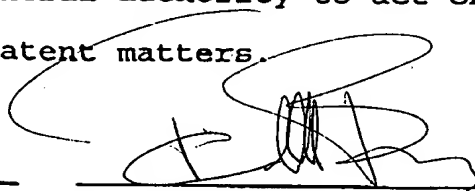
1. ENTER THE NUMBER OF DAYS FOR THE TESTING PHASE AS DEFINED IN 37 CFR 1.775(c) (1)		1621	
2. ENTER THE NUMBER OF DAYS FOR THE APPROVAL PHASE AS DEFINED IN 37 CFR 1.775(c) (2)		1620	
3. ADD LINE 1 AND 2 AND ENTER THE TOTAL HERE			3241
4. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT		0	
5. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d) (1) (ii)		0	
6. ADD LINE 4 AND LINE 5 AND ENTER THE TOTAL HERE			0
7. SUBTRACT LINE 6 FROM LINE 5 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")			3241
8. ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT		294	
9. ENTER THE NUMBER OF DAYS		0	
10. ADD LINE 8 AND LINE 9 AND ENTER THE TOTAL HERE			294
11. SUBTRACT LINE 10 FROM LINE 7 AND ENTER THE DIFFERENCE HERE			2947
12. ENTER THE NUMBER OF DAYS FROM LINE 1		1621	
13. ENTER THE NUMBER OF DAYS FROM LINE 10		294	
14. SUBTRACT LINE 13 FROM LINE 12 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")		1327	
15. MULTIPLY LINE 14 BY 0.5 (ONE HALF) AND ENTER THE AMOUNT HERE			664
16. SUBTRACT LINE 15 FROM LINE 11 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")			2283
17. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT		7-12-2005	
18. ENTER THE EXPIRATION DATE OF PATENT IF EXTENDED BY THE NUMBER OF DAYS ON LINE 16		10-23-11	
19. ENTER THE DATE OF THE FDA (FOOD AND DRUG ADMINISTRATION) FINAL APPROVAL		5-23-1997	
20. LIMITATION SET FORTH IN 37 CFR 1.775(d) (3)		14 YEARS	
21. ADD THE NUMBER OF YEARS ON LINE 20 TO THE DATE ON LINE 19 AND ENTER THE REVISED DATE HERE		5-23-11	
22. ENTER THE EARLIER DATE APPEARING ON LINE 18 OR LINE 21			5-23-11
23. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)		7-12-05	
24. CHECK ONE OF THE FOLLOWING THREE BOXES AND ENTER THE LISTED TIME PERIOD HERE		5 years	
	THE PATENT ISSUED AFTER 09/24/84	5 YEARS	
X	THE PATENT ISSUED PRIOR TO 09/24/84 AND NO REQUEST FOR EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (i) WAS FILED PRIOR TO 09/24/84	5 YEARS	
	THE PATENT ISSUED PRIOR TO 09/24/84 AND AN EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (ii) WAS FILED PRIOR TO 09/24/84	2 YEARS	
25. ADD THE NUMBER OF YEARS ON LINE 24 TO THE DATE ON LINE 23 AND ENTER THE REVISED DATE HERE		7-12-10	
26. ENTER THE EARLIER DATE APPEARING ON LINE 22 OR LINE 25			7-12-10
27. ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)			7-12-05
28. ENTER THE NUMBER OF DAYS BY WHICH LINE 26 AND LINE 27 DIFFER HERE THIS IS THE LENGTH OF THE PATENT TERM EXTENSION			1820

POWER OF ATTORNEY



I, Fredrik Berg, Company Secretary of Pharmacia & Upjohn AB, hereby appoint Burton A. Amernick, of the firm Pollock, Vande Sande & Priddy, 1990 M Street, NW, Suite 800, Washington, DC 20036, as attorney with general authority to act on behalf of Pharmacia & Upjohn AB in patent matters.

Date: July 10, 1997



Fredrick Berg
Company Secretary
Pharmacia & Upjohn AB

CONFIDENTIAL

NDA #20-227

9 September 1992

RD HEPARIN (ARDEPARIN) SODIUM INJECTION
10,000 Anti-Factor Xa Units/mL
20,000 Anti-Factor Xa Units/mL

EXHIBIT

12

ALL-STATE® INTERNATIONAL

I. Drug Substance

A. Description, Including Physical and Chemical Characteristics and Stability

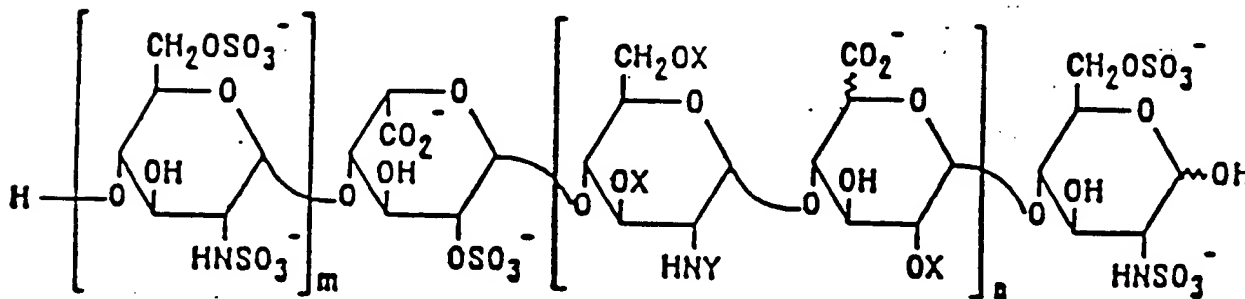
1. Names

Established (generic name): RD Heparin Sodium; low molecular weight heparin sodium; ardeparin sodium (USAN).

Descriptive Chemical Name: Polymers of derivatives of D-glucosamine (N-sulfated, N-acetylated, and/or O-sulfated) and hexuronic acid (L-iduronic acid or D-glucuronic acid; including O-sulfated derivatives).

Low Molecular Weight Heparin Code Numbers:
WY-90,493 and WY-90,505.

2. Structural Formula



$m=0 \text{ or } 1$

$n=7-9$

$X=H, SO_3^-$

$Y=SO_3^-, COCH_3$

The molecular weight range for RD Heparin is such that not less than 98% falls within 2,000 - 15,000 Daltons with a weight average of 5,500 - 6,500 Daltons.